In Appreciation of Lawrence C. Katz, 1956–2005

Larry Katz

Larry Katz, the James B. Duke Professor of Neurobiology at Duke University and an Investigator of the Howard Hughes Medical Institute, died on November 25, 2005 from melanoma. He was a pioneer in the analysis of visual system development and a new leader in functional analysis of the olfactory system. Larry's trademark was the brilliant technological innovation that suddenly made impossible experiments possible.

Larry trained in animal behavior, electrophysiology, and neuroanatomy, and from the beginning was always thinking of a better way to do things. As an undergraduate, his first love was behavior. With Richard Wassersug in Chicago, he analyzed the behavior of *Xenopus* tadpoles as they made parallel formations and hung midwater before swimming in schools. Wassersug was stumped as to how to study this behavior in the dark. "In three nanoseconds, Larry exclaimed, 'we can use a flash and camera!'. I would have spent days in arriving at the answer," reported Wassersug. Similar moments would happen many times in his career. Larry was a technophile with a love of sports cars, airplanes, and any kind of lab equipment—he was happiest when he could build an entirely new apparatus to do an experiment.

As a work-study student with Ray Guillery in Chicago, a graduate student with Mark Konishi at Caltech, and a postdoc with Torsten Wiesel at the Rockefeller University, Larry came to embrace the importance of neuroanatomy in understanding the brain. He developed dazzling neuroanatomical approaches at the frontier of the scientific questions of the day and available technology.

Konishi recalls:

> I vividly remember when Larry arrived at my home after driving from Chicago. After he parked his car, he went under it to fix something. I was much impressed by this episode, because he gave the impression that he was a man of action. Everything he did later proved that my impression was correct…. I had enough "wild" kids who would do anything. Larry Katz was the most adventurous and skillful. I was so charmed by him that I would allow him to rent a small airplane to fly to Stanford to get a new histological tracer. Next, he suggested that we introduce brain slice techniques. So, he and I drove down to UC Irvine to see slice setups. On our way home, we bought a couple of components, which Larry assembled into a functioning system within a few days.

(This system resembled a finely-honed hardboiled egg slicer.)

With Konishi, Larry developed powerful new methods to study the anatomical organization of neural tissues by retrograde tracing. Fluorescent latex microspheres, his particular pet, are still widely used in neuroanatomy. He injected tracers into a target area, allowed the processes to take up the tracer and transport it back to their cell bodies, sliced the tissues, and examined the location of the tracer. Applying these methods to cat visual cortex, he showed that cortical neurons projecting to different targets have different, and characteristic, axon and dendrite morphologies. The specificity of connectivity he discovered in this work had important implications for cortical visual processing. If each class of projection neuron in the cortex had characteristic anatomical inputs and outputs, then each class was likely to carry a discrete kind of visual information (Katz, 1987; Katz et al., 1984).

Almost in passing, from another set of experiments in Konishi's lab, Larry and Mark Gurney published the first paper that demonstrated auditory responses in the song nuclei of zebra finches (Katz and Gurney, 1981). His science opened many doors.

Larry was a postdoc and then an Assistant Professor at Rockefeller. There he met an undergraduate, Doris Iarovici, who would become a psychiatrist and writer, and his wife. They married in 1989 and have two children, Ariel, 12, and Justin, 9.

At Rockefeller, Larry's interest in anatomy shifted to mechanism: how did these elaborate axonal and dendritic arbors develop? How was connectivity between neurons specified among the many choices in the cortex? Which aspects of development were encoded by molecular templates, and which were shaped by visual input? Torsten Wiesel, who with David Hubel and colleagues had made the first discovery that visual experience can alter the structure of the brain, was a mentor and colleague through these studies.

Using fine-scale anatomical tracing, Larry and his colleague Ed Callaway examined the development of long horizontal connections between neurons in the visual cortex that prefer similar orientations. They showed that an initial crude map was refined through process elimination and that visual deprivation degraded the accuracy of refinement. By contrast, the arborization of axons in cortical layers appeared accurate from the outset. The first wiring rules were appearing.

Anatomy constrains, but does not completely define, the connections between neurons. Recognizing the limitations of anatomy for studying local circuitry, Callaway and Katz developed the method of laser scanning photostimulation, a higher-throughput technique for connectivity mapping by physiology (Callaway and Katz, 1993). In laser scanning photostimulation, neural circuitry is analyzed by releasing caged glutamate at different locations with light pulses while recording from a postsynaptic neuron far from the site of glutamate release. Glutamate stimulates neurons where it is released, and the subsequent response of the postsynaptic cell shows what kind of connections exist between the two different regions. This combined optical and electrophysiological method is of increasing significance now, when solving circuitry has returned to prominence in neuroscience.

Larry's early anatomical and physiological studies spawned many areas of developmental neuroscience. The full impact of his discoveries about connectivity and development is still unfolding: for example, with Yuste and Peinado, Larry discovered that neurons in the developing cortex are highly interconnected by gap junctions, which disappear later in development (Yuste et al., 1992). The role of these connected domains in the formation of cortical circuits remains a mystery.

After moving to Duke, Larry's lab asked what kinds of molecules might be involved in the changes in axon and dendrite structure that occur during development. He was one of the pioneers in studying dendrite and spine remodeling, which are now widely studied in functional plasticity as well as developmental plasticity. His lab developed methods for gene transfer along with dye transfer into brain slices as a way to manipulate and observe the morphologies of single neurons. With his student Kim McAllister and colleague Donald Lo, Larry showed that neurotrophins stimulate the growth of dendrites in brain slice cultures and that different neurotrophins preferentially stimulate the growth of basal or apical dendrites on different classes of cortical neurons (Figure 2). The idea that neurotrophins could have region-specific and cell type-specific effects on morphology began to create a molecular vocabulary for neuronal morphogenesis.

In the early 1990s, thinking about the neurotrophins moved from a classical view of their role in neuronal survival to a view that local use of neurotrophins might represent a signal for plasticity and development. In particular, the hypothesis emerged that neurons might compete for limiting amounts of neurotrophins that would stimulate local growth and somehow encourage the neurons with the right activity patterns. Larry and David Riddle showed that "losing" thalamocortical neurons that wither after activity blockade can be rescued by precise delivery of neurotrophins to the cortex (Riddle et al., 1995). With a cleverly devised stimulation protocol, Larry and Michael Weliky then clinched views about activity-based competition by changing cortical orientation tuning by artificially correlating activity patterns (Weliky and Katz, 1997). With respect to the link between activity and neurotrophins, Larry and colleagues provided a key observation by showing that only active neurons respond to neurotrophins with dendrite growth (McAllister et al., 1996). This result provided one of the first conceptual links between biochemical factors and electrical activity and showed that the abstract principles from classical developmental and physiological studies could have simple molecular explanations.

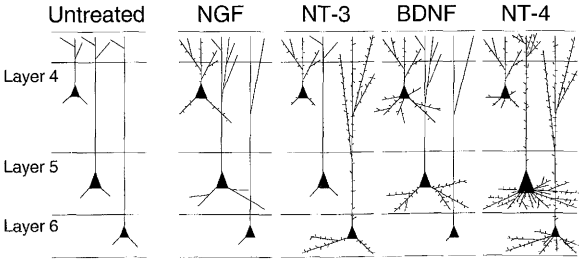

Figure 2. Neurotrophin Effects on Pyramidal Neurons in Developing Visual Cortex

Different neurotrophins have cell-type specific and region-specific effects on dendrite length, branching, and spines. From McAllister et al. (1995).

McAllister remembers Larry as an advisor:

> Larry exposed me to the idea that experience alters connectivity within the brain during development. This basic concept was fascinating to Larry and is still quite extraordinary to me… Beyond his published work, Larry's passion for this topic was truly infectious. He loved thinking about how activity could alter the structure of neurons. He loved the challenge of intractable issues.

The entangled roles of activity and innate maps in development remained an active area in Larry's lab. In the visual system, there was a widely-held view that ocular dominance columns—the regions of the cortex that preferentially respond to the left eye or right eye—were defined entirely from the bottom up, through retinal activity-dependent sorting of axons. Using high-resolution anatomical methods, Larry and Justin Crowley showed that wiring information intrinsic to the brain needed to be taken into account (Crowley and Katz, 1999, 2000). They found that developing connections between the lateral geniculate nucleus of the thalamus (LGN) and the cortex begin to segregate into distinct domains very early, before retinal inputs provide different patterns of activity to the LGN. Segregation of stripes between LGN and cortex could occur even without retinal input. These results suggest that a prepattern of LGN-cortex stripes cooperates with patterned activity from the eye to shape the developing visual system. From this work emerges a picture in which multiple levels of the visual system, from the retina to the cortex, interact to refine visual system organization.

In the late 1990s, a new research area on olfaction emerged in Larry's lab. Advances in molecular biology were providing a new look at odor processing, and, for the first time, a way to categorize and identify the many cell types in the olfactory system. Larry was the first to integrate this new molecular information with physiology and anatomy.

His first advance was to provide a systems-level analysis of the organization of the olfactory bulb. Molecular biology had brought the message that neurons expressing a single odorant receptor project to olfactory glomeruli in a pattern that is reproducible from animal to animal. What did the glomeruli process? Larry applied

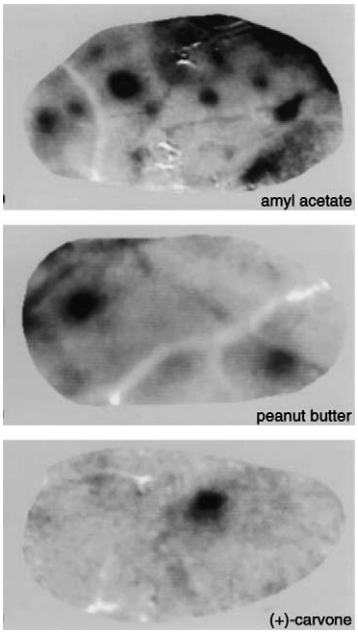

Figure 3. Intrinsic Signal Imaging of Odorant Responses in the Olfactory Bulb of Live Rats

Some odors activate many glomeruli (top) and others only one glomerulus (bottom) in the imaged region. From Rubin and Katz (1999).

intrinsic signal imaging to the olfactory bulb for the first time, allowing him to visualize the activity of many glomeruli simultaneously in live animals exposed to odors (Figure 3). He found that the patterns were largely reproducible but not identical from individual to individual, as suggested by the molecular data. Intrinsic signal imaging helped define the general rules for odor detection. Prior to Larry's work, it was appreciated that odor recognition by receptors was combinatorial, but it was unclear whether a single odor typically activated 1% or 50% of all receptors and glomeruli. Larry's imaging data showed that most natural odors—even complex odors like beer and peanut butter—activate a relatively small fraction of the glomeruli.

Larry's lab then combined molecular biology in transgenic mice, innovative imaging methods, and electrophysiology to ask how the olfactory bulb interprets odor information. They showed that glomeruli in the olfactory bulb have a center-surround organization where activation of one glomerulus tends to inhibit nearby glomeruli. They discovered a new class of interneurons that specifically connect glomeruli that detect the same odors, even when those glomeruli are widely separated in the olfactory bulb. They addressed structural plasticity, using two-photon microscopy to follow dendrites in olfactory glomeruli over weeks; these dendrites formed scaffolds that remained remarkably stable during the extensive neurogenesis and turnover of synaptic connections that occurs in the olfactory system.

Larry's career had begun in behavior and came full circle to return to behavior in the olfactory system of rodents. Rodents are olfactory animals whose mating and aggressive behaviors are strongly regulated by olfactory cues. Larry and his colleagues Minmin Luo and Michael Fee asked how this occurred by examining neurons in the accessory olfactory bulb, which is implicated in social and sexual behaviors. Recording from single neurons in the accessory olfactory bulb of behaving male mice, they showed that they are activated by interactions with other mice (Figure 4). Each neuron responded to a specific combination of the sex of the target mouse and its strain identity, suggesting that the vomeronasal/accessory olfactory bulb system encodes specific social information about other individuals.

Most recently, Larry and his colleagues combined biochemistry and physiology to discover a mouse social pheromone—purifying a single, vanishingly rare molecule from mouse urine based on its ability to stimulate olfactory neurons (Lin et al., 2005). This work initiated a re-evaluation of the roles of the main olfactory system and the vomeronasal system by showing that the main olfactory system senses pheromones relevant for mating. His work surprised and amazed to the last.

Larry's work was recognized with numerous awards, beginning with his Ph.D. thesis, which won the Clauser prize for the most original thesis from Caltech. He received the Society for Neuroscience Young Investigator Award and the Charles Judson Herrick Award of the American Association of Anatomists.

Larry was a tremendous colleague who formed strong and lasting relationships with his mentors and advisors, his close and distant scientific colleagues, and his own students and junior colleagues at Duke. He counted

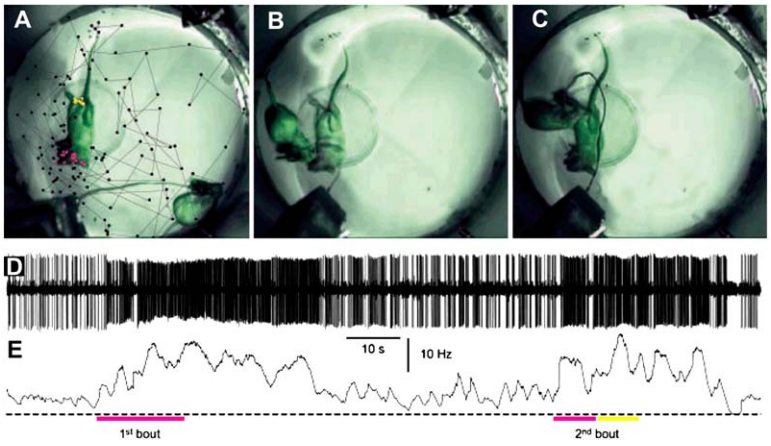

Figure 4. Neurons in the Accessory Olfactory Bulb (AOB) Recognize Conspecific Individuals

(A) Tracks of a behaving mouse interacting with a sleeping target mouse. (B and C) Snapshots of interactions. (D) Spiking response and (E) average response of one AOB neuron in the behaving mouse as it sniffs the target mouse's head (pink) or tail (yellow). Reprinted with permission from Luo et al. (2003).

Larry fishing, June 2005

among his scientific mentors Mark Konishi, Torsten Wiesel, and his colleagues Carla Shatz and Richard Axel. He in turn was a skilled and generous mentor, and imparted to his many successful students his belief "that hard work, creativity, and persistence could conquer the most difficult technical hurdle" (K. McAllister). Larry enjoyed scientists as well as science and had a seemingly unlimited number of friends of all ages. He had a memory for the telling detail that let him tell hilarious stories about his colleagues.

Many scientists recognize the importance of communicating with the lay world; Larry acted on it. He brought a measure of levity to the serious business of neuroscience by publishing a book appreciated by aging baby boomers, "Keeping Your Brain Alive: 83 Neurobic Exercises", written with Manning Rubin and published by Workman Press in 1999. Playfully extending his own findings on how activity could elicit release of neurotrophins, he delivered recipes for using the five senses in novel ways to encourage new neural connections to form and to combat memory loss.

Passion, energy, and a love of adventure were Larry's motifs in science and in life. He loved fishing, travel, flying airplanes. He loved literature and the arts, his family and friends.

His friend Rich Lewis recalls his scientific philosophy:

> His motivation was really based on a sense of curiosity about nature rather than a desire to cure a particular disease, or to work on something that was popular at the time. He was naturally drawn to areas that were out of the mainstream, where he could make a unique contribution.

Shortly before his death, Stuart Firestein saw Larry:

> He talked about the future—where Neuroscience was going, where he would like to see it go, what were the critical issues in olfaction, how to run searches and how find the best new faculty. I have never experienced such mental toughness. He knew the score and determined to go on living as he had because that's who he was.

Neuroscience has lost a creative mind and some of its joy.

Acknowledgments

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